TABLE 383-2 PREVALENCE OF EXTRAGLANDULAR MANIFESTATIONS IN PRIMARY SJÖGREN'S SYNDROME

Clinical Manifestation	Percent	Remarks
Arthralgias/arthritis	60	Usually non-erosive, leading to Jaccoud's arthropathy.
Raynaud's phenomenon	37	In one-third of patients, precedes sicca manifestations.
Lymphadenopathy	14	Lymphoma should be excluded.
Lung involvement	14	Small airway disease is the predominant pathology.
Vasculitis	11	The most common clinical manifestation is cutaneous palpable purpura.
Kidney involvement	9	Interstitial kidney disease is usually asymptomatic. Glomerulonephritis is associated with cryoglobulinemia.
Liver involvement	6	Primary biliary cirrhosis stage I.
Lymphoma	6	Glandular MALT[a] lymphoma is most common.
Peripheral neuropathy	2	Polyneuropathy, either sensory or sensorimotor.
Myositis	1	Sporadic causes of myositis and inclusion body myositis have been reported.

[a]Mucosa-associated lymphoid tissue.

arthritis. Patients with primary Sjögren's syndrome more often report easy fatigability, low-grade fever, Raynaud's phenomenon, myalgias, and arthralgias. Most patients with primary Sjögren's syndrome experience at least one episode of non-erosive arthritis during the course of their disease. Manifestations of pulmonary involvement are frequently evident histologically but are rarely important clinically. Dry cough is the major manifestation that is attributed to small airway disease. Renal involvement includes interstitial nephritis, clinically manifested by hyposthenuria and renal tubular dysfunction with or without acidosis. Untreated acidosis may lead to nephrocalcinosis. Glomerulonephritis is a rare finding that occurs in patients with mixed cryoglobulinemia or with systemic lupus erythematosus overlapping with Sjögren's syndrome. Vasculitis affects small and medium-sized vessels. The most common clinical features are purpura, recurrent urticaria, skin ulcerations, glomerulonephritis, and mononeuritis multiplex.

Different autoantibodies may determine the clinical expression of the disease. Patients positive for anticentromere autoantibody present with a clinical picture similar to that of limited scleroderma (Chap. 382). Antimitochondrial antibodies may connote liver involvement in the form of primary biliary cirrhosis (Chap. 369). Autoantibodies to 21-hydroxylate have recently been described in almost 20% of patients; their presence is associated with a blunted adrenal response.

Central nervous system involvement is rarely recognized. A few cases of myelitis associated with antibody to aquaporin 4 have been described.

Lymphoma is a well-known manifestation of Sjögren's syndrome that usually presents later in the illness. Persistent parotid gland enlargement, purpura, leukopenia, cryoglobulinemia, low C4 complement levels, and ectopic germinal centers in minor salivary gland biopsy samples are manifestations suggesting the development of lymphoma. It is interesting that the same risk factors account for glomerulonephritis and lymphoma and that these risk factors are the ones that confer increased mortality risk. Most lymphomas are extranodal, low-grade marginal-zone B cell lymphomas and are usually detected incidentally during evaluation of the labial biopsy. The affected lymph nodes are usually peripheral. Survival rates are decreased in patients with B symptoms, lymph node mass >7 cm in diameter, and high or intermediate histologic grade.

Routine laboratory tests in Sjögren's syndrome reveal mild normochromic, normocytic anemia. An elevated erythrocyte sedimentation rate is found in ~70% of patients.

TABLE 383-3 DIFFERENTIAL DIAGNOSIS OF SICCA SYMPTOMS

Xerostomia	Dry Eye	Bilateral Parotid Gland Enlargement
Viral infections	Inflammation	Viral infections
Drugs	Stevens-Johnson syndrome	Mumps
Psychotherapeutic	Pemphigoid	Influenza
Parasympatholytic	Chronic conjunctivitis	Epstein-Barr virus
Antihypertensive	Chronic blepharitis	Coxsackievirus A
Psychogenic origin	Sjögren's syndrome	Cytomegalovirus
Irradiation	Toxicity	HIV, HCV
Diabetes mellitus	Burns	Sarcoidosis
Trauma	Drugs	IgG4 syndrome
Sjögren's syndrome	Neurologic conditions	Sjögren's syndrome
Amyloidosis	Impaired lacrimal gland function	Metabolic disorders
	Impaired eyelid function	Diabetes mellitus
	Miscellaneous	Hyperlipoproteinemias
	Trauma	Chronic pancreatitis
	Hypovitaminosis A	Hepatic cirrhosis
	Blink abnormality	Endocrine
	Anesthetic cornea	Acromegaly
	Lid scarring	Gonadal hypofunction
	Epithelial irregularity	

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

Primary Sjögren's syndrome is diagnosed if (1) the patient presents with eye and/or mouth dryness, (2) eye tests disclose keratoconjunctivitis sicca, (3) mouth evaluation reveals the classic manifestations of the syndrome, and/or (4) the patient's serum reacts with Ro/SS-A and/or La/SS-B autoantigens. Labial biopsy is needed when the diagnosis is uncertain or to rule out other conditions that may cause dry mouth or eyes or parotid gland enlargement (Tables 383-3 and 383-4). Validated diagnostic criteria have been established by a European study and have now been further improved by a European-American study group (Table 383-5). Hepatitis C virus infection should be ruled out since, apart from serologic tests, the clinicopathologic picture is almost identical to that of Sjögren's syndrome. Enlargement of major salivary glands, particularly in seronegative patients, should raise the suspicion of IgG4-related syndrome, which may present also as chronic pancreatitis, interstitial nephritis, retroperitoneal fibrosis, and aortitis.

TREATMENT SJÖGREN'S SYNDROME

Treatment of Sjögren's syndrome is aimed at symptom relief and limitation of the damaging local effects of chronic xerostomia and keratoconjunctivitis sicca through substitution for or stimulation of the missing secretions (Fig. 383-1).

TABLE 383-4 DIFFERENTIAL DIAGNOSIS OF SJÖGREN'S SYNDROME

HIV Infection and Sicca Syndrome	Sjögren's Syndrome	Sarcoidosis
Predominant in young males	Predominant in middle-aged women	No age or sex preference
Lack of autoantibodies to Ro/SS-A and/or La/SS-B	Presence of autoantibodies	Lack of autoantibodies to Ro/SS-A and/or La/SS-B
Lymphoid infiltrates of salivary glands by CD8+ T lymphocytes	Lymphoid infiltrates of salivary glands by CD4+ T lymphocytes	Granulomas in salivary glands
Association with HLA-DR5	Association with HLA-DR3 and DRw52	Unknown
Positive serologic tests for HIV	Negative serologic tests for HIV	Negative serologic tests for HIV